Thorax 1999;**54**:268–272

How much asthma is really attributable to atopy?

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In recent decades it has become routine to describe asthma as an atopic disease. A theoretical paradigm has evolved in which allergen exposure produces atopic sensitisation and continued exposure leads to clinical asthma through the development of airways inflammation, bronchial hyperresponsiveness, and reversible airflow obstruction. As Martinez[1] notes, this paradigm has been used with particular insistence with regard to house dust mite allergens,[2 3] but other allergens (cat, cockroach, dog) are also believed to be important. The importance of atopy is most widely accepted for asthma in children whereas, among adults, asthma has traditionally been divided into "extrinsic" and "intrinsic" asthma, although this also has been challenged.[4] It is acknowledged that not all cases of asthma fit this paradigm—for example, some occupational causes of asthma do not appear to involve atopy—but these are regarded as interesting minor anomalies that do not threaten the dominant paradigm.

In this review we assess the extent to which the development of asthma is attributable to atopy (we do not consider the separate issue of the extent to which the development of atopy itself is attributable to allergen exposure, although this is also the subject of debate[1]). We start by considering definitions of asthma and atopy and then review evidence on their association in random population surveys. We do not intend to argue that atopy does not play an important role in the development of a significant proportion of asthma cases. However, our concern is that the proportion of asthma cases attributable to atopy may have been overestimated, and that other possible aetiological mechanisms and risk factors for asthma may therefore have been neglected.

Definitions of asthma and atopy

The definition of asthma is still controversial but an appropriate definition is a precondition for addressing the issues considered in this paper. The term "asthma" encompasses a disparate group of disorders which produce similar clinical effects—that is, variable airflow obstruction[5]—and this has formed the basis of the definition of asthma.[6 7] Some current definitions also emphasise the importance of airways inflammation,[8] although the relationship between airways inflammation and variable airways obstruction is not straightforward.[9–12] In some studies asthma has been defined more restrictively in terms of the immunological or pathophysiological mechanisms by which variable airflow obstruction is presumed to have occurred—for example, atopy or bronchial hyperresponsiveness (BHR). However, this leads to a significant proportion of asthma cases being excluded, and the relationship between "asthma" and atopy or BHR then becomes merely tautological. Thus, asthma is best defined in terms of the phenomena involved—that is, variable airflow obstruction—without making any restrictions based on possible aetiological considerations.[13 14] For these reasons we have focused on studies that used physician diagnoses of asthma or self-reported asthma or asthma symptoms. We did not use definitions of asthma based on BHR since this would also lead to a considerable proportion of asthma cases being excluded,[15] and because BHR is part of the causal model that we are assessing (in fact, atopy is more strongly associated with BHR than it is with airflow variability[16]).

"Atopy" has previously been used as a poorly defined term to refer to allergic conditions which tend to cluster in families, including hay fever (allergic rhinitis), asthma, eczema, and other specific and non-specific allergic states.[17] More recently, atopy has been characterised by the production of specific IgE in response to common environmental allergens,[18] and skin prick testing provides a convenient test for atopy in epidemiological studies.[19] However, it has been suggested that total serum IgE provides an overall estimate of the allergic component in asthma,[4] and that total serum IgE is associated with asthma independently of specific IgE levels.[20] In this review we therefore focus on studies of skin prick test positivity, but we also consider studies of total serum IgE levels.

To assess the association of atopy with asthma in individuals and in populations we conducted a Medline search from 1980 onwards for English language publications of studies that contained at least one of the key words "hypersensitivity, immediate", "hypersensitivity", "IgE", or "skin tests". From these we selected epidemiological studies on asthma ("asthma" combined with "cross-sectional studies", "case-control studies", "longitudinal studies" or "prevalence"; or "respiratory tract disease/epidemiology"; or "asthma/epidemiology"; or "bronchitis/epidemiology"). We then selected only population based studies with a source population of at least 600 subjects (in some instances these were prevalence case-control studies and the total number of cases and controls was less than 600, even though the source population was larger than 600). For the reasons noted above we excluded studies that used BHR in their definition of asthma. We also excluded studies which did not report the proportions with atopy or with raised total serum IgE levels among cases and non-cases, and studies using IgE levels measured before the age of one year. For studies with multiple publications we only used one report.

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Table 1 Percentage of asthma cases attributable to atopy (defined as at least one positive skin prick test) in population based studies

Reference	Age	Non-asthmatics No.	Non-asthmatics Atopy (%)	Asthmatics No.	Asthmatics Atopy (%)	Relative risk	% of cases attributable to atopy	Definition of asthma
Studies exclusively or predominantly in children								
Gergen *et al*[21]	6–17	5505	21	395	45	3.1	30	Diagnosis or frequent wheezing
Burrows *et al*[4]	6–34	994	44	89	79	4.8	63	"Asthma" + symptoms
Sears *et al*[22]	13	399	35	315	57	2.5	34	Clinical examination
Norrman *et al*[23]	14	887	40*	110	66	2.5	40	Ever asthma
Von Mutius *et al*[24]	9–11†	4756	37	274	69	3.8	51	Diagnosis with current symptoms
	9–12‡	2523	18	100	40	3.0	27	Diagnosis with current symptoms
Martinez *et al*[25]	6	442	35	187	56	2.3	32	Persistent or late onset wheeze
Brooke *et al*[26]	4–9	220	26	54	54	3.3	38	Current wheeze
Sporik *et al*[27]	12–14	53	64	67	73	1.5	25	Respiratory symptoms
Remes and Korppi[28]	7–12	204	46	43	77	3.8	57	Clinical examination
Studies exclusively or predominantly in adults								
Burrows *et al*[4]	35–54	498	40	47	72	3.9	53	Asthma with symptoms
	55+	928	23	101	40	2.2	22	Asthma with symptoms
Mensinga *et al*[29]§	17–49	2711	26	94	46	2.4	27	Asthma attacks ever
Sparrow *et al*[30]¶	41–86	598	23	28	29	1.4	8	Adult onset wheeze
Wüthrich *et al*[31]	18–60	7789	21*	568	56	4.8	44	Diagnoses
Settipane *et al*[32]¶	40–42	654	35	36	56	2.4	32	Asthma attacks
Bodner *et al*[33]	39–45	217	45	102	55	1.5	18	Adult onset wheeze
Siracusa *et al*[34]	0–69	783	19	41	63	7.3	55	Current diagnosed asthma

*Estimated.
†West Germany.
‡East Germany.
§Atopy definition based on skin prick index (no. of positive reactions × size of weals).
¶Prospective study, age at end of follow up.
All studies are based on a source population of at least 600 subjects but some prevalence case-control studies involve smaller numbers of cases and controls.

Association of atopy with asthma in individuals

The proportion of asthma cases that are "attributable" to atopy (defined as skin prick test positivity) can be estimated by the "population attributable risk". If exposure has an odds ratio for asthma of R (the odds ratio is the appropriate measure to use in prevalence studies and prevalence case-control studies[15]), then the proportion of exposed cases that are attributable to exposure is (R—1)/R, and the proportion of all cases in the population that are attributable to exposure (population attributable risk) is P(R—1)/R where P is the proportion of all cases that are exposed.

SKIN PRICK TEST POSITIVITY

The proportions of asthmatic and non-asthmatic subjects who are skin prick test positive vary considerably between different studies[4 21–34] (table 1). The weighted mean of the estimates from these studies, mostly conducted in Western countries, indicates that overall about 58% of children and 54% of adults with asthma were skin prick test positive; however, about 29% of non-asthmatic children and 24% of non-asthmatic adults were also skin prick test positive. The proportion of cases attributable to atopy varied from 25% to 63% in cross-sectional studies exclusively or predominantly in children, with a weighted mean of about 38%; in studies exclusively or predominantly in adults, the population attributable risk varied from 8% to 55% with a weighted mean of 37%. Thus, the population attributable risk was similar in children and adults, but it should be emphasised that these studies were not all done in the same populations and, in fact, studies performed within a single population (for example, reference 4) found higher attributable risks in children than in adults.

It might be argued that the definition of skin prick test positivity used in these studies is too weak or non-specific since it is based on "at least one positive skin test" from a range of allergens. We therefore considered data from Sears *et al*[22] because this publication included the necessary information and the population attributable risk of atopy for asthma in this study (34%) was similar to the average for all studies in children in table 1 (38%). Table 2 shows that, as the definition of atopy (in terms of the number of positive skin prick test responses) is strengthened, the association with asthma also strengthens—that is, the odds ratio increases—but the population attributable risk decreases from 34% to 3% because of the reduction in the proportion of the population that is "positive". Thus, when a more "severe"

Table 2 Percentage of asthma cases attributable to atopy based on number of positive skin prick tests and specific skin prick tests

Skin prick tests*	% Non asthmatics atopic (n =399)	% Asthmatics atopic (n =315)	Relative risk	% of cases attributable to atopy
No. of positive tests				
1+	35.1	57.1	2.5	34
2+	16.5	40.6	3.5	29
3+	7.3	27.3	4.8	22
4+	2.0	14.3	8.1	13
5+	1.0	9.8	10.8	9
6+	0.5	7.0	14.9	7
7+	0.3	2.9	11.7	3
Specific skin prick tests				
Any positive test	35.1	57.1	2.5	34
Rye grass	23.4	44.4	2.6	27
House dust mite	19.4	43.7	3.2	30
Cat	5.5	23.2	5.2	19
Alternaria	4.5	8.6	2.0	4
Dog	2.2	9.9	4.9	8
Horse	1.8	10.2	6.3	9
Cladosporium	1.3	5.7	4.7	4
Kapok	1.5	4.1	2.8	3
Aspergillus fumigatus	0.5	4.8	9.7	4
Wool	0.8	4.4	6.0	4
Penicillium	2.0	2.5	1.3	1

*Defined as the development of weals at least 2 mm greater than negative control.
Adapted from Sears *et al*.[22]

Table 3 Percentage of asthma cases attributable to atopy (defined as a total serum IgE level of 100+ IU/ml) in population based studies

		Non-asthmatics		Asthmatics				
Reference	*Age*	*No.*	*Atopy (%)*	*No.*	*Atopy (%)*	*Relative risk*	*% of cases attributable to atopy*	*Definition of asthma*
Burrows *et al*[4]	6–34	994	30	89	73	6.3	61	"Asthma" + symptoms
	35–54	498	18	47	57	6.0	48	"Asthma" + symptoms
	55+	928	13	101	34	3.5	24	"Asthma" + symptoms
Remes and Korppi[28]	7–12	204	45	43	38	0.7	–16	Clinical examination
Sears *et al*[35]	11	500	46	62	89	9.5	80	Diagnosed current asthma
Burrows *et al*[36]*	15+	2255	12	160	38	4.5	30	Current diagnosed asthma
Sunyer *et al*[20]	20–44	1761	25	155	50	3.0	33	Asthma attack ever
Bodner *et al*[33]	39–45	217	13	102	23	2.0	11	Adult onset wheeze

*Atopy defined as a total serum IgE level of 160+ IU/ml.

definition of atopy is used—for example, four or more positive skin prick tests—the association with asthma (as reflected in the relative risk estimate) increases, but the proportion of cases that are atopic (according to the more severe definition) decreases and the population attributable risk decreases. Similar analyses for the allergen-specific test results (table 2) showed that some specific allergens had stronger associations with asthma, but that the highest estimate of the population attributable risk (34%) is obtained with "any positive skin test".

SERUM IgE

An obvious limitation of these data is that skin prick testing uses a wide range of allergens believed to be predominant in the area under study, but it will not necessarily identify all cases of atopy. It is therefore important also to consider atopy as defined in terms of total serum IgE, since it has been suggested that it provides an overall estimate of the allergic component in asthma[4] and because it is more readily comparable between studies. Table 3 summarises the studies of total serum IgE[4 20 28 33 35 36] and shows that the population attributable risk of atopy (defined as a raised total serum IgE level) for asthma varied from less than 0% (an inverse association) to 80% with a weighted mean of 33%.

Once again, these findings depend on the cut off point that is used to define atopy, and Burrows *et al*[4] have argued that some type of IgE mediated process may be involved in almost all asthma cases, even when skin test reactivity to common allergens is not found. Thus, if a more liberal definition of atopy (in terms of raised serum IgE levels) is used, a higher proportion of asthmatic subjects might be considered to be atopic. Table 4 shows data from Burrows *et al*[36] with the attributable risk estimates that would be obtained using different cut off points for serum IgE. Once again this study was chosen because it reported the relevant information, and because the population attributable risk of atopy for asthma in this study (30%) was similar to the weighted average for all studies (33%). The proportion of cases attributable to atopy continues to increase as the definition of atopy is "loosened" but, even using the most liberal definition (in which 85% of non-asthmatic patients and 95% of asthmatic patients are considered to be atopic), only about two thirds of the asthma cases are attributable to atopy.

Table 4 Percentage of asthma cases attributable to atopy, using different cut off levels for total serum IgE

Serum IgE level (IU/ml)	*% Non asthmatics atopic (n =2255)*	*% Asthmatics atopic (n =160)*	*Relative risk*	*% of cases attributable to atopy*
640+	3.5	15.6	5.2	13
320+	7.0	26.9	4.9	21
160+	11.7	38.1	4.6	30
80+	25.0	56.3	3.9	42
40+	41.4	71.3	3.5	51
20+	57.1	81.3	3.3	56
10+	72.4	90.0	3.4	64
5+	84.8	95.0	3.4	67

Adapted from Burrows *et al.*[36]

These findings are likely to be underestimates because non-differential misclassification of atopy and/or asthma will usually bias the relative risk estimate towards the null value.[15] On the other hand, the association between total serum IgE and asthma may in part, at least in some cases, simply be an association rather than reflecting a causal link. In particular, Sunyer *et al*[20] have suggested that: co-inherited genetic factors could increase susceptibility both to asthma and to the production of raised serum IgE levels; total serum IgE levels could in part be a consequence of asthma itself and could be a marker of non-allergic inflammation; or that IgE could also express a humoral autoimmunity since specific reactivity against human proteins structurally similar to allergens has been described. In each of these situations the association between total serum IgE and asthma would not be entirely causal, and the findings presented here would therefore be overestimates.

Association of atopy with asthma in populations

It is also of interest to consider the associations of the atopy measures with asthma prevalence at the population level, particularly in light of the global increases[37] and the substantial international differences[38 39] in the prevalence of asthma.

Table 5 summarises studies, identified from the same Medline search used for table 1, in which asthma and atopy (skin prick test positivity) were measured in the same population at different times, or in two or more different populations at the same time. Although a few studies suggest an association between the prevalence of atopy and asthma (Charpin *et al*,[40] Wieringa *et al*[45]), most studies do not. For example, Peat *et al*[42] found little or no association between the prevalence of atopy

Table 5 Prevalence of skin prick test positivity and asthma in population based studies comparing different populations or the same population over time

Reference	*Population*	*No.*	*Age*	*% with +ve skin prick test*	*% with doctor diagnosed asthma or 'asthma'*
Comparisons of populations					
Charpin *et al*[40]	Marseille	4008	18–65	28*	4
	Briancon	1055	18–65	10*	2
Von Mutius[24]	Munich	4451	9–11	37	9
	Leipzig/Halle	2335	9–11	18	7
Leung and Ho[41]	Malaysia	321	16	64	3
	Hong kong	471	14	58	7
	China	647	16	49	2
Peat *et al*[42]	Sydney	1339	8–11	42	24
	West Sydney	904	8–11	42	28
	Moree/Narrabi	770	8–11	40	31
	Wagga Wagga	850	8–11	40	29
	Belmont	926	8–11	39	38
	Broken Hill	794	8–11	37	30
	Lismore	805	8–11	35	31
Nowack *et al*[43]	Hamburg	1159	20–44	36	2
	Erfurt	731	20–44	30	1
Yemaneberhan[44]	Rural Ethiopia	861	5–70+	12*	1
	Urban Ethiopia	2194	5–70+	4*	4
Wieringa *et al*[45]	Urban Antwerp	319	20–44	26*	7
	Suburban Antwerp	337	20–44	17*	4
Comparisons of time periods					
Peat *et al*[46]	Busselton 1981	553	18–55	39	9
	Busselton 1990	1028	18–55	41	16
Peat *et al*[47]	Belmont 1982	718	8–10	28	9
	Belmont 1992	873	8–10	29	38
	Wagga Wagga 1982	769	8–10	30	13
	Wagga Wagga 1992	795	8–10	35	30
Von Mutius *et al*[48]	Leipzig/Halle 1991/2	1492	9–11	19	4
	Leipzig/Halle 1995/6	2311	9–11	27	4

*Skin prick positivity to house dust mites.

and diagnosed asthma in different parts of Australia.

Similarly, Leung and Ho[41] reported that asthma prevalence was high in Hong Kong (7% for asthma ever), intermediate in Malaysia (3%), and low in San Bu, China (2%), but atopy prevalence was similar in the three centres (58%, 64% and 49%, respectively).

Yemaneberhan *et al*[44] reported major differences in the prevalence of asthma between rural (1%) and urban (4%) populations in southwest Ethiopia. However, skin prick test positivity to house dust mites was more common in rural (12%) than in the urban (4%) areas; there was little difference in the prevalence of skin prick positivity to other allergens such as mixed threshings or *Aspergillus* (not shown in table).

There is evidence of an association of the prevalence of atopy with the prevalence of asthma in the studies showing higher levels of both in Western than in Eastern Europe.[24] However, no increase in the prevalence of asthma was observed among East German children between 1991 and 1996, although the prevalence of atopy increased from 19% to 27%.[48] On the other hand, Peat *et al*[46 47] found marked increases in diagnosed asthma in Busselton, Belmont, and Wagga Wagga, Australia (there were similar but less dramatic increases in the 12 month period prevalences of wheezing, not shown in table), but there was little change in the prevalence of atopy in these three centres (table 5).

The European Community Respiratory Health Survey[49] has not yet fully published its results, but the prevalence of atopy (defined as raised specific serum IgE levels) appears to be associated with the prevalence of subjects reporting asthma attacks[38] at the country level. However, this association is mainly driven by the English speaking countries with other European countries showing only a weak association, and no association has been observed between the prevalence of asthma and total serum IgE levels.[49]

Conclusions

The available epidemiological evidence suggests that the population based proportion of asthma cases that are attributable to atopy is usually less than one half. Higher estimates (up to two thirds) can be obtained by using very low cut off levels of total serum IgE, but these should be interpreted with caution since such a definition of atopy has limited practical use, and these associations may not always be causal. Moreover, standardised comparisons across populations or time periods show only a weak and inconsistent association between the prevalence of asthma and the prevalence of atopy. These findings indicate that the importance of atopy as a cause of asthma in individuals may have been overemphasised. The danger is that overemphasis on a particular theoretical paradigm for which the evidence is less substantial than is commonly assumed may have led to an under-recognition of, and insufficient research into, other possible aetiological mechanisms for the development of asthma.

The Wellington Asthma Research Group is supported by a Programme Grant from the Health Research Council of New Zealand and by a major grant from the Guardian Trust (Trustee of the David and Cassie Anderson Medical Charitable Trust). Juha Pekkanen was supported by the Academy of Finland.

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